REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow are respectfully requested.

Claims 1-18 are pending in the application.

By the above amendment, claim 1 has been amended to further define the claimed composition as comprising an amount of at least 1 agent sufficient to elicit an irritant side effect to a user when utilized in a composition that does not include and interleukin-1 antagonist or a TNF-alpha antagonist wherein the irritant agent is an active agent in said composition. Claim 1 has been further amended to define the composition as comprising an amount of at least one compound, selected from an identified group, sufficient to prevent or alleviate said irritant side effect. Support for this amendment can be found at least at pages 14-15 of the English language translation of the specification. Additionally, claim 2 has been amended to more broadly define the active agent in the composition of claim 1.

Turning now to the Official Action, claims 1-18 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,658,581, over claims 1-20 of U.S. Patent 5,993,833, over claims 1-30 of U.S. Patent No. 6,277,387 and over claims 15-41 of U.S. Patent No. 6,060,061. In response to the Examiner's rejection over claims 1-7 of U.S. Patent No. 5,658,581 and claims 39-41 of U.S. Patent No. 6,060,061, Applicants have filed appropriate terminal disclaimers together with the instant Amendment to obviate these rejections.

With respect to the rejection over claims 1-20 of U.S. Patent No. 6,993,833 and over claims 1-30 of U.S. Patent No. 6,277,387, Applicants provide the following remarks. Applicants submit that because claims 1-20 of U.S. Patent No. 6,993,833 and claims 1-30 of U.S. Patent No. 6,277,387 are method claims defining a method for the treatment of sensitive skin, the composition claims of the instant application, directed to a composition for pharmaceutical, cosmetic or dermatological usage, are clearly patentably distinct from the claims of the '833 and '387 patents. Accordingly, Applicants submit that these rejections are improper and should be withdrawn.

Claims 1-2, 4, 8, 10-11, 13 and 17 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. For at least the reasons that follow, withdrawal of these rejections is in order.

With respect to the rejection of claims 2 and 11 for use of the term "solvents," Applicants have amended claims 2 and 11 to obviate this rejection. More specifically, Applicants have amended claims 2 and 11 to remove the remove the word "solvents."

With respect to the rejection of claims 1 and 10 for use of the phrase "one agent which produces an irritant side-effect," Applicants have amended claims 1 and 10 to obviate this rejection. More specifically, Applicants have amended claims 1 and 10 to read in part "...an amount of at least one agent sufficient to elicit an irritant side-effect...."

With respect to the rejection of claims 4 and 13, Applicants submit that the claims 4 and 13, and the disclosure at page 8, paragraph 32 are intended to disclose that the antagonist of the invention are, for example, compounds that comprise at least one

heterocycle and nitrogen compounds comprising at least benzene ring. That is, the "at least one benzene ring" limitation applies only to nitrogen compounds.

With respect to the rejection of claims 8 and 17 for use of the phrase "agents which modulate the differentiation and/or the proliferation and/or the pigmentation of skin," Applicants submit that these terms would be readily understood by one of ordinary skill in the art when read in view of the specification. That is, the specification at page 13, paragraph 56, provides examples of specific agents which modulate differentiation and/or proliferation and/or skin pigmentation, such as retinoic acid and its isomers, retinol and its esters, vitamin D and its derivatives, estrogens such as estrodial, kojic acid or hydroquinone etc.

For at least the above reasons, reconsideration and withdrawal of the rejection is in order.

Claims 1-2, 5-8, 10-11 and 14-17 stand rejected under 35 U.S.C. §102(b) as being anticipated by *Parker et al.* (U.S. Patent No. 5,039,695). For at least the reasons that follow, withdrawal of the rejection is in order.

The present invention relates to the use of a histamine antagonist, an interleukin-1 antagonist and/or TNF-alpha antagonist in a cosmetic pharmaceutical or dermatological composition for topical application, intended, in particular, for the treatment of sensitive skin, as well as to a composition containing a histamine antagonist, and interleukin-1 antagonist and/or a TNF-alpha antagonist for the purpose of decreasing or even abolishing the irritant effects of certain products, and in particular of certain active agents used in the

cosmetics, pharmaceutical or dermatological field. See specification at page 1, paragraph 2.

For example, independent claim 1, as amended above, sets forth a composition suitable for pharmaceutical, cosmetic or dermatological usage said composition comprising an amount of at least one agent sufficient to elicit an irritant side-effect to a user when utilized in a composition that does not include an interleukin-1 antagonist or a TNF-alpha antagonist, and wherein said irritant agent is an active agent in said composition, an amount of at least one compound selected from the group consisting of interleukin-1 antagonists, TNF-alpha antagonists and combinations thereof, sufficient to prevent or alleviate said irritant side-effect, and a cosmetically, dermatologically or pharmaceutically acceptable medium therefor.

It is well established, that in order to establish anticipation under §102(b), each element of the claim in issue must be found, either expressly described or under principles of inherency, in a single prior art reference. Kalman v. Kimberly-Clark Corp., 218 USPQ 789 (Fed. Cir. 1983). That is not the case here.

Parker relates to certain aryl- and heteroaryl-alkyl-pyrrole carboxylic acid compounds of the formula I and to salts thereof. Additionally, *Parker* is related to the pharmacological use of the compounds of formula I as interleukin-1 inhibitors effective in alleviating interleukin-1 mediated conditions. See *Parker* at col. 1, line 55 to col. 2, line 9.

Parker does not disclose or suggest each feature of the presently claimed invention. For example, *Parker* does not disclose or fairly suggest a composition comprising at least

one agent sufficient to elicit an irritant side-effect to a user when utilized in a composition that does not include an interleukin-1 antagonist and/or a TNF-alpha antagonist, an amount of at least one compound selected from the group consisting of interleukin-1 antagonist, TNF-alpha antagonist and combination thereof, sufficient to prevent or alleviate said irritant side-effect, and a cosmetically, dermatologically or pharmaceutically acceptable medium therefor, as set forth, for example, in independent claim 1.

In particular, *Parker* discloses that the compound of formula I can be administered with a pharmaceutically-acceptable carrier using conventional dosage unit forms parenternally, orally, topically, or the like. See *Parker* at col. 8, lines 7-11. Additionally, *Parker* discloses that the disclosed compositions can be preserved by adding an antioxidant such as ascorbic acid or other suitable preservatives. See *Parker* at col. 11, lines 11-14. In stark contrast, the composition of the presently claimed invention, requires a combination of at least one IL-1 antagonist and/or at least one TNF-alpha antagonist and at least one active agent that elicits a desired effect in the composition.

The composition of the presently claimed invention further requires that the active agent be contained in an amount sufficient to cause irritation to a user but for the presence of the at least one IL-1 antagonist and/or the at least one TNF-alpha antagonist. Accordingly, the composition of the presently claimed invention includes specific amounts of both IL-1 antagonist and/or TNF-alpha antagonist and active agent. That is, the irritant active agent must be contained in an amount sufficient to cause irritation and the IL-1 antagonist and/or TNF-alpha antagonist must be present in an amount sufficient to alleviate

and/or prevent the irritation caused by the irritant active agent. Clearly, *Parker* fails to disclose or fairly suggest such a combination. That is, nowhere does *Parker* specifically disclose or suggest a composition comprising an active agent that elicits an irritant side-effect to a user of the composition.

Also, *Parker* is further deficient in that Parker fails to meet the functional limitations of the presently claimed invention. As discussed above, the composition of the presently claimed invention is specifically defined in the claims as including an amount of irritant active agent sufficient to elicit irritation to a user and an amount of IL-1 antagonist and/or TNF-alpha antagonist sufficient to alleviate or prevent such irritation. Accordingly, Applicants submit that the composition of *Parker* would not include the specific ratio of irritant relative to IL-1 antagonist and/or TNF-alpha antagonist, as claimed.

Additionally, the preservative (i.e., ascorbic acid as an antioxidant preservative) does not constitute an active agent as defined in the presently claimed invention. That is, the ascorbic acid preservative of *Parker* does not constitute an agent sufficient to elicit an irritant side-effect to a user when used in a composition that does not include an interleukin-1 antagonist or a TNF-alpha antagonist.

For at least these reasons, the composition of the presently claimed invention is not anticipated by *Parker*. Accordingly, withdrawal of the §102(b) rejection based on *Parker* alone is respectfully requested.

Claims 1-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Parker* in view of *Blank et al.* (U.S. Patent No. 5,605,894). For at least the reasons that follow, withdrawal of the rejection is in order.

As explained above, *Parker* fails to disclose or fairly suggest each and every feature of the presently claimed invention. That is, *Parker* clearly fails to disclose or suggest a composition comprising a combination of an irritant active agent present in an amount sufficient to elicit irritation to a user and a IL-1 antagonist and/or TNF-alpha antagonist present in an amount sufficient to alleviate or prevent irritation caused by the irritant active agent.

Additionally, *Parker* discloses that there is a need to control the release of IL-1 and IL-1 mediated conditions and inflammation without production of concomitant side effects which presently accompany the use of anti-inflammatory steroids and non-steroidal anti-inflammatory agents. See *Parker* at col. 1, lines 45-52. Accordingly, the objective of *Parker* is to provide better IL-1 inhibitors. *Parker* achieves this objective by providing compounds of formula I as IL-1 inhibitors that are effective in alleviating IL-1 mediated conditions. In stark contrast to the composition of the presently claimed invention, nowhere does *Parker* disclose or even suggest providing a IL-1 inhibitor in a composition to antagonize an irritant side-effect elicited by an active agent present in the composition. Accordingly, *Parker* clearly fails to disclose or suggest the composition of the presently claimed invention, as set forth, for example, in claims 1 and 3.

Blank fails to overcome the above deficiencies of *Parker*. *Blank* relates to the field of anti-aging of skin. In particular, the invention of *Blank* relates to novel compositions for effacing and preventing wrinkles in the mammalian skin. See *Blank* at col. 1, lines 10-14.

For example, claim 1 of *Blank* defines a composition for regulating wrinkles and atrophy in mammalian skin comprising treating the skin with (a) a safe and effective amount of salicylic acid, (b) another active component and (c) a pharmaceutically acceptable carrier.

Blank discloses that the objective of the disclosed invention is to combat irritation caused by salicylic acid. In particular, *Blank* discloses that salicylic acid is known to be used for the treatment of various conditions. *Blank* further discloses that because salicylic acid is often used in large doses, it can cause significant irritation and is incompatible with a persistent treatment of normal skin. See *Blank* at col. 1, lines 46-52. Thus, the objective of *Blank* is to provide compositions for regulating wrinkles and/or atrophy in mammalian skin compatible with a persistent treatment of normal skin. *Blank* achieves this objective by providing a composition comprising (a) a safe and effective amount of an anti-wrinkle/anti-atrophy agent, (b) a safe and effective amount of an additional compound, and (c) a pharmaceutically acceptable carrier. According to *Blank*, a "safe and effective amount" is intended to mean an amount of compound sufficient to induce a positive modification in the condition to be treated, but low enough to avoid serious side effects. See *Blank* at col. 2, lines 40-44.

Among other additional compounds, Blank discloses that anti-inflammatory agents can be included in the composition along with the active compound (salicylic acid). *Blank* further discloses that the inclusion of an anti-inflammatory agent enhances the wrinkle regulating benefits of the composition. *Blank* further discloses that the anti-inflammatory agent is believed to provide strong protection against UVA radiation thereby preventing further wrinkle formation caused by UV irradiation. Thus, the combination disclosed in *Blank* is intended to provide broad antiwrinkle protection. See *Blank* at col. 5, lines 3-14.

Clearly, *Blank* is substantially directed to providing a salicylic acid comprising composition that is compatible with persistent treatment of normal skin aging. In this context, *Blank* discloses that this objective is achieved by providing a composition comprising both salicylic acid and anti-inflammatory agent because the latter will enhance the wrinkle regulating benefits of the composition. That is, *Blank* discloses using an anti-inflammatory agent in the disclosed composition as an additional compound for the anti-inflammatory agent's antiwrinkle properties. *Blank* does not disclose or fairly suggest a composition comprising a combination of at least one IL-1 antagonist and/or TNF-alpha antagonist and at least one active agent that elicits a desired effect in the composition. Additionally, *Blank* fails to further require that the composition comprise an active agent in an amount sufficient to cause irritation to a user but for the presence of the at least one IL-1 antagonist and/or at least one TNF-alpha antagonist.

Like *Parker*, *Blank* also fails to disclose or fairly suggest a composition that meets the functional limitations of the presently claimed composition. That is, because Blank fails to disclose or suggest a combination of IL-1 antagonist and/or TNF-alpha antagonist and an active agent, Applicants submit that the composition of *Blank* would not contain the ratio of irritant relative to IL-1 antagonist and/or TNF-alpha antagonist present in the composition of the presently claimed invention.

Applicants submit that it is noteworthy that even though *Blank* discloses using benzofuran derivatives, *Blank* only discloses including benzofuran derivatives to increase the wrinkle regulating benefits of the disclosed composition. See *Blank* at col. 7, lines 40-41. In stark contrast to the composition of the presently claimed invention, *Blank* fails to disclose or even suggest including an anti-inflammatory agent in the disclosed composition for its ability to antagonize an irritant side effect produced by an active agent present in the composition, as defined in the independent claims. Moreover, *Blank* neither discloses nor suggests including a sufficient amount of at least one IL-1 and/or a TNF-alpha antagonist and/or at least a histamine antagonist in the disclosed composition for the ability of such antagonist to antagonize irritant side effects of an active agent present in the composition.

For at least these reasons, the composition of the presently claimed invention would not have been obvious over *Parker* in view of *Blank*. Accordingly, withdrawal of the §103(a) rejection over *Parker* in view of *Blank* should be withdrawn.

Claims 1-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Blank* in view of *Skotnicki* (U.S. Patent No. 4,902,800). For at least the reasons that follow, withdrawal of the rejection is in order.

For at least all the reasons explained above, *Blank* fails to disclose or suggest the composition of the presently claimed invention.

Skotnicki fails to overcome the above deficiencies of *Blank*. *Skotnicki* relates to novel compounds possessing interleukin 1 (IL-1) antagonist activity and having anti-inflammatory activity. See *Skotnicki* at col. 1, lines 5-7.

In particular, *Skotnicki* discloses that the disclosed compounds can be administered alone or by combining them with conventional carriers. See *Skotnicki* at col. 3, lines 36-38. *Skotnicki* also discloses that the formulation of the disclosed compound is adapted for topical administration. See *Skotnicki* at col. 3, lines 52-56.

Generally, the objective of *Skotnicki* is to provide novel compounds having IL-1 antagonist activity. *Skotnicki* achieves this objective by providing novel compounds corresponding to 1-substituted-4-pyrolidinopiperidines. *Skotnicki* fails to disclose or suggest a composition comprising a combination of at least one IL-1 antagonist and/or at least one TNF-alpha antagonist and at least one active agent that elicits a desired effect, as set forth, for example, in independent claim 1. Additionally, *Skotnicki* fails to further disclose a composition comprising an active agent contained in an amount sufficient to cause irritation to a user but for the presence of the at least one IL-1 antagonist and/or at least one TNF-alpha antagonist. Like *Parker* and *Blank*, *Skotnicki* also fails to disclose or

fairly suggest a composition that meets the functional limitations of the presently claimed invention. That is, the composition of *Skotnicki*, like both *Parker* and *Blank*, also would not include the ratio of irritant relative to IL-1 antagonist and/or the TNF-alpha antagonist present in the composition of the presently claimed invention.

For at least these reasons the composition of the presently claimed invention would not have been obvious over *Blank* in view of *Skotnicki*. Accordingly, withdrawal of the §103(a) rejection over *Blank* in view of *Skotnicki* is respectfully requested.

As a final note Applicants have amended the specification to provide a more accurate English language translation of the French priority document. That is, Applicants have amended the Application and claims by replacing the words "inflammation" and "sensations of inflammation" with the words --overheating-- and --sensations of overheating-- respectively.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

If there are any questions concerning this paper or the Application in general, the Examiner is invited to telephone the undersigned at the Examiner's earliest convenience.

Respectfully submitted,

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Attachment to Amendment dated December 20, 2001
Mark-up of the Abstract

The invention relates to the use of a histamine antagonist, an interleukin-1 antagonist and/or a TNF-alpha antagonist in a cosmetic, pharmaceutical or dermatological composition for treating sensitive skins. It relates especially to the use of a histamine antagonist, an interleukin-1 antagonist and/or a TNF-alpha antagonist for preventing and/or combating skin irritations and/or sores and/or erythema and/or dysaesthesic sensations and/or sensations of [inflammation] overheating and/or pruritus and/or prickling and/or tingling and/or discomfort and/or tightness of the skin and/or mucosae. It also relates to a composition containing a histamine antagonist, an interleukin-1 antagonist and/or a TNF-alpha antagonist which limits or eliminates the irritant side-effects of certain products, and in particular of certain cosmetic, dermatological or pharmaceutical active agents.

Attachment to Amendment dated December 20, 2001
Mark-up of the Specification.

Paragraph number 7

--The Applicants have carried out numerous clinical tests and have been able to determine the symptoms associated with sensitive skins. These symptoms are, in particular, subjective signs which are essentially dysaesthesic sensations. Dysaesthesic sensations are understood to mean more or less painful sensations experienced in an area of the skin, such as prickling, tingling, itching or pruritus, burning, [inflammation,] overheating, discomfort, tightness, and the like.--

Paragraph number 11

--An intolerant skin is a skin which reacts by sensations of [inflammation] overheating or of tightness, by pruritus, that is to say by itching or prickling, by tingling and/or red blotches, to different factors such as the environment, emotions and foods. In general, these signs are associated with erythema and with a skin with or without sores. --

Paragraph number 12

--"Sensitive" scalps have a more unequivocal symptomatology: the sensations of pruritus and/or of prickling and/or of [inflammation] overheating are essentially triggered by local factors such as rubbing, soap, surfactants, hard water with a high chalk concentration, shampoos or lotions. These sensations are also sometimes triggered by

Attachment to Amendment dated December 20, 2001
Mark-up of the Specification.

factors such as the environment, emotions and/or foods. Erythema and hyperseborrhoea of the scalp as well as a dandruff state are frequently associated with the above signs.--

Paragraph number 13

--Moreover, in some anatomical regions, such as the major folds (inguinal, genital, axillary, popliteal, anal and inframammary regions, bend of the elbow) and the feet, sensitive skin manifests itself in pruriginous sensations and/or dysaesthesic sensations ([inflammation] overheating, prickling) associated especially with sweating, with rubbing, with wool, with surfactants, with hard water with a high chalk concentration and/or with temperature changes.--

Paragraph number 20

--In addition, the Applicants found that the addition of interleukin-1 antagonists and/or of TNF-alpha antagonists to cosmetic, pharmaceutical or dermatological compositions for topical application containing irritant products (alpha-hydroxy acids, retinoids, benzoyl peroxide, etc.) also enabled the irritation reactions usually caused by these products to be decreased or even eliminated. These irritation reactions manifest themselves within moments following application, in dysaesthesic sensations ([inflammation] overheating, burning, itching or pruritus sensations, prickling sensations, tightness, etc.), and/or in red blotches, and/or in edema. These irritation states may also

Attachment to Amendment dated December 20, 2001
Mark-up of Claims 1 and 2

1. (Amended) A composition suitable for pharmaceutical, cosmetic or dermatological usage, said composition comprising:

= an amount of at least one agent [which produces] sufficient to elicit an irritant side-effect[,] to a user when utilized in a composition that does not include an interleukin-1 antagonist or a TNF-alpha antagonist, and wherein said irritant agent is an active agent in said composition,

= an amount of at least one compound selected from the group consisting of interleukin-1 antagonists, TNF-alpha antagonists and combinations thereof, [in an amount effective] sufficient to [antagonize] prevent or alleviate said irritant side-effect, and a cosmetically, dermatologically or pharmaceutically acceptable medium therefor.

2. (Amended) The composition of Claim 1, wherein the agent which produces an irritant side-effect is selected from the group consisting of alpha-hydroxy acids, beta-hydroxy acids, alpha-keto acids, beta-keto acids, retinoids, anthralins, anthranoids, peroxides, minoxidil, lithium salts, antimetabolites, vitamin D[,] and depigmentation agents[, solvents, perfumes, preservatives, surfactants and alcoholic solutions].